REMARKS

Claims 53-64 were pending in the instant application. Claims 53-56, 59 and 61-62 have been amended and claims 63 and 64 has been canceled. Accordingly, claims 53-62 and 65 will be pending after entry of the instant amendment has been entered. Support for the claim amendments can be found throughout the specification and claims as originally filed. Support for new claim 65 can be found at page 22, line 18-19 of the specification. No new matter has been added.

Any amendments to and/or cancellation of the claims was done solely to more particularly point out and distinctly claim the subject matter of Applicant's invention to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or in a separate application(s).

Objection to the Amendment Filed January, 25, 2001 Under 35 U.S.C. 132

The Examiner has objected to the amendment filed January 25, 2001 under 35 U.S.C. 132. The Examiner states that the amendment "introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: (e.g., PPPSS trunc MEKK, PPPSS corresponding to amino acids 211 to 215 of SEQ ID NO:2)."

Applicant respectfully traverses this rejection. The specification as filed contained the term PPPSS-trunc, e.g., in Example 15 at page 94. The amendment filed on January 25, 2001 merely specified the residue numbers of SEQ ID NO:2 that correspond to the Pro-Pro-Pro-Ser-Ser sequence set forth in the specification. Accordingly, since PPPSS-trunc is disclosed in the specification and SEQ ID NO:2 is presented in the sequence listing filed with the application, the amendment submitted on January 25, 2001 does not constitute new matter.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the foregoing objection.

Objection to Claims 59-64 as Being Directed to Non-Elected Inventions

The Examiner has objected to claims 59-64 because "they pertain to the use of non-elected invention of the nucleic acid of SEQ ID NO:s: 1, 3, 5, 7, 9, 11, 13 and the polypeptide of SEQ ID NOs:6, 8,10, 12 and 14." Applicants have amended claims 53 and 61-64 so as to be

directed to only SEQ ID NOs:2 and 4, or the nucleic acid molecules that encode these polypeptides, thereby rendering this objection moot.

Objection to the Sequence Listing

The Examiner has objected to the sequence listing because "[t]his application fails to comply with the sequence rules, 37 CFR 1.821-1.825." The Examiner further indicates that "[n]ucleotide and polypeptide sequences must be identified with the corresponding SEQ ID NO. Title 37, Code of Federal Regulations, Section 1.821 states 'reference must be made to the sequence by use of the assigned identifier', the identifier being SEQ ID NO. There are numerous sequences contained in the specif[i]cation, e.g. on pages 13, 45, 49, 69, 72, which have not been identified by SEQ ID NO. Their corresponding SEQ ID NO must identify sequences present in the specif[i]cation so as to comply with the sequence rules."

Applicants have amended the specification to incorporate SEQ ID NOs where appropriate and have revised the sequence listing accordingly. Applicant submits herewith a substitute diskette containing the sequence listing a paper copy of the sequence listing. Applicant states that the content of the paper copy and the content of the computer readable form are identical as required by 37 CFR 1.821(e).

Rejection of Claims 53-58 Under 35 U.S.C. 112, Second Paragraph

The Examiner has objected to claims 53-58 under 35 U.S.C. 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner is of the opinion that

> [c]laims 53, 54, 55, and 56 are indefinite because the name MEKK protein does not provide any structural limitations and the metes and bounds of the claim cannot be determined. It is unclear what structure encompasses MEKK protein. It is unclear what structure encompasses nucleic acid encoding said MEKK protein. It is suggested, to overcome the rejection, MEKK protein and nucleic acid be identified by SEQ ID NO.

Applicants have amended the claims to indicate that the MEKK molecules used in the claimed methods are MEKK molecules having SEQ ID NOs: 1 or 2. Accordingly, these claims are clear and definite. Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

The Examiner has also rejected claims 53 because "it is not clear what activity of the MEKK protein is regulated in the cell such that apoptosis of the cell is regulated, so as to allow the metes and bounds of the claim cannot be determined." Claim 53 has been amended to indicate that the agent modulates the activity of an MEKK 1 polypeptide in a cell such that apoptosis of the cell is regulated. Applicant's specification clearly teaches that expression of MEKK 1 polypeptides in a cell induces apoptosis. For example, Example 19B teaches that cells expressing MEKK 1 polypeptides underwent cytoplasmic shrinkage and nuclear condensation leading to apoptotic death. Further, Example 20A demonstrates that microinjection of an expression plasmid encoding of $MEKK_{COOH}$, a truncated activated form of MEKK1, results in apoptosis. Accordingly, Applicant has clearly shown that MEKK1 expression leads to apoptosis. Applicant is not required to elucidate the exact mechanism by which apoptosis occurs in order to satisfy the conditions of patentability. Therefore, based on the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw this rejection.

The examiner has further rejected claims 54 and 55 because "are indefinite because it is not clear what activity of the kinase domain of MEKK protein is regulated, so as to allow the metes and bounds of the claim [to] be determined." Specifically, the Examiner states that it

> is not clear which fragment of MEKK contains the critical structural feature of the invention to be classified as the kinase domain of MEKK protein. Also, it is not clear which fragment of MEKK contains the critical structural feature of the invention to be classified as the regulatory domain of MEKK protein.

And further, regarding claim 56,

> it is not clear which fragment of MEKK contains the critical structural feature of the invention to [be] classified as the kinase catalytic domain of MEKK protein. Although the proteins of SEQ ID NOs 2 and 4 contain regions of the kinase catalytic domain of MEKK protein it is not clear at what amino acid said domain starts and end, so as to allow the metes and bounds of the claim cannot be determined.

Applicant respectfully traverses this rejection.

Applicant has amended the claims to be directed to MEKK 1 molecules. Applicant's specification teaches the exact location of the kinase and regulatory domains of representative MEKK1 molecules, e.g., MEKK1.1 and MEKK1.2 set forth at SEQ ID NOs:2 and 4,

respectively. For example, Applicant teaches at page 30, lines 16-21, that the kinase domain is located between residues 409 and 672 of MEKK 1.1 and between residues 1331 and 1594 of MEKK 1.2. The specification further teaches at page 30, lines 17-28 that the regulatory domain is located between residues 1 and 408 of MEKK1.1 and between residues 1 and 1328 of MEKK1.2.

The activity of a kinase domain is well known to one of skill in the art. A literature search demonstrates that as far back as 1952 people were doing detailed mechanistic studies on kinases. Therefore, there is no doubt that the activity of a kinase is well known to one of ordinary skill in the art. Moreover, Applicant teaches specific activities and targets of the kinase domain of MEKK. For example, Applicant's specification teaches at page 16, lines 9-13, that the MEKK molecules of the invention interact with, and directly phosphorylate members of the MAP kinase kinase family (MEKs or MKKs), MEK1, MEK2, MKK1, MKK2, or the stress-activated kinases (SEKs), and the Jun kinase kinases (JNKK1, JNKK2, MKK3, MKK4). Furthermore, Applicant teaches at page 49, lines 24-27 of the specification that MEKK1 is capable of binding to Ras and that the binding occurs via the COOH kinase domain.

The Examiner's rejection of claims 57 and 58 as being dependent on an indefinite base claims should be obviated by the amendments and remarks presented herein.

Based on the teachings available in the specification and the knowledge available to one of ordinary skill in the art, the ordinary skilled artisan would find the claims to be clear and definite. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 53-58 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claims 53-58 under 35 U.S.C. 112, first paragraph, because "the specification, while being ***enabling for a method for regulating cell apoptosis comprising contacting the cell with an agent that binds to MEKK protein of SEQ ID NO:2 or 4 or the truncated MEKK disclosed in Example 15***, wherein said agent regulates the ability of said MEKK to be phosphorylated or to phosphorylate a substrate such as MAP kinase or other substrate disclosed in the Examples such that apoptosis of the cell is regulated, it does not reasonably provide enablement for other MEKKs or agents that stimulate MEKK activity."

The claims have been amended such that they are limited to MEKK 1 molecules, i.e., polypeptides of SEQ ID NOs:2 and 4, and nucleic acid molecules set forth as SEQ ID NOs:1 and 3. Accordingly, this rejection as it pertains to other MEKK molecules is rendered moot.

Applicant respectfully traverses this rejection as it pertains to agents that stimulate MEKK activity. Applicant's specification provides multiple working examples of molecules that stimulate MEKK activity and further provide a number of assays that one of skill in the art would use to screen molecules for the ability to stimulate MEKK molecules, e.g., MEKK 1 molecules. For example, Figures 5 and 6 depict the results of experiments described in Example 8, that demonstrate that both NGF and EGF stimulate MEKK activity. Applicant further provides two references that indicate that MEKK activity can be stimulated by Ras (see page 107, lines 5-7 of the specification where Russell, M. et al. (1995) J. Biol. Chem. 270:11757-11760; and Winston, B.W., et al. (1995) Proc. Natl. Acad. Sci. USA (1995) 92:1614-1618 are cited).

In addition to the working examples cited above, Applicant has provided assays that one of skill in the art would use to test for the ability of an agent to stimulate MEKK molecules. For example, Applicant provides Example 9 in which assays for measuring the stimulation of MEKK by growth factors are taught. Applicant also provides MEKK induced apoptosis assays that can be used to monitor the stimulation of MEKK1 (see, for example, page 96, lines 9-21 of the specification).

Accordingly, based on the teachings and working examples set forth in the specification, the ordinary skilled artisan would be able to make and use the claimed invention using only routine experimentation.

Rejection of Claims 53-58 Under 35 U.S.C. 112, First Paragraph

The Examiner has rejected claims 53-58 under 35 U.S.C. 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner states

> [c]laims 53-59 encompasses use of polypeptide/proteins variants of the protein identified as MEKK, said variants may be completely unrelated, structurally and functionally to use of the protein disclosed in SEQ ID NO:2 and 4. The

name MEKK protein does not provide any structural limitations nor does it identify the critical feature of the invention.

Applicants respectfully traverse this rejection.

The claims have been amended to be directed to methods using MEKK1 molecules having SEQ ID NOs:2 or 4, or the nucleic acid molecules that encode these polypeptides. Accordingly, all claimed molecules are MEKK1 molecules set forth as SEQ ID NOs: 1, 2, 3 or 4, or molecules with a high level of sequence identity to these MEKK1 molecules. Further, all claims are have a functional limitation that further defines the critical features of the molecules used in the claimed methods, i.e., the ability to regulate apoptosis.

Moreover, as indicated above, the location of both the regulatory domain and catalytic domain are set forth in the specification. Applicant's specification teaches the location of the kinase and regulatory domains of representative MEKK1 molecules, e.g., MEKK1.1 and MEKK1.2 set forth at SEQ ID NOs:2 and 4, respectively. For example, Applicant teaches at page 30, lines 16-21, that the kinase domain is located between residues 409 and 672 of MEKK 1.1 and between residues 1331 and 1594 of MEKK 1.2. The specification further teaches at page 30, lines 17-28 that the regulatory domain is located between residues 1 and 408 of MEKK1.1 and between residues 1 and 1328 of MEKK1.2.

Accordingly, the disclosure provides description of the polypeptide and nucleic acid molecules used in the claimed methods such that one of skill in the art would find the claims to be adequately described such that the ordinary skilled artisan would understand that Applicant was in possession of the claimed invention at the time of filing the application.

Art Made of Record But Not Relied Upon

The Examiner has cited database PIR 78 (Accession Number A39723) but has not relied upon this record. Applicants would like to make of record that the cited reference describes a sequence that shares very low sequence similarity to the molecules claimed in the instant methods and, further, PIR 78 does not have the same biological function as the molecules claimed in the instant methods. Accordingly, this reference does not affect the patentability of the instant claims.

IDS

The Examiner has asked that Applicant disclose in which application each reference cited in the IDS filed on April 15, 2003 was previously cited. Accordingly, every reference cited in the IDS was cited in the parent application USSN: 09/608,890 (Issued as U.S. Patent No.: 6,333,170 on December 25, 2001).

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this statement. However, if a fee is due, please charge our Deposit Account No. 12-0080, under Order No. CPI-004DVCP3CN from which the undersigned is authorized to draw.

Dated: November 18, 2004

Respectfully submitted,

By_____

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